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Double standards in special medical research: questioning the discrepancy between requirements for medical research involving incompetent adults and medical research involving children

Medical research represents a substantial departure from conventional medical care. Medical care is patient-orientated, with decisions based on the best interests and/or wishes of the person receiving the care. In contrast, medical research is future-directed. Primarily it aims to contribute new knowledge about illness or disease, or new knowledge about interventions, such as drugs, that impact upon some human condition. Current State and Territory laws and research ethics guidelines in Australia relating to the review of medical research appropriately acknowledge that the functions of medical care and medical research differ. Prior to a medical research project commencing, the study must be reviewed and approved by a Human Research Ethics Committee (HREC). For medical research involving incompetent adults, some jurisdictions require an additional, independent safeguard by way of tribunal or court approval of medical research protocols. This extra review process reflects the uncertainty of medical research involvement, and the difficulties surrogate decision-makers of incompetent adults face in making decisions about others, and deliberating about the risks and benefits of research involvement. Parents of children also face the same difficulties when making decisions about their child's research involvement. However, unlike the position concerning incompetent adults, there are no similar safeguards under Australian law in relation to the approval of medical research involving children. This column questions why this discrepancy exists with a view to generating further dialogue on the topic.

INTRODUCTION

Recent media coverage by the *New York Times* has focused on the conduct of United States researchers involved in a clinical study of oxygenation levels in extremely low birth weight infants.[1] This coverage has highlighted the ethical uncertainties that arise when there is a blurring of the boundary between experimental research and therapy in paediatrics, particularly where parents have responsibility for making difficult decisions about the care of their child. This column outlines some of the legal and ethical issues relevant to the Australian context, with a view to generating further debate.

A RECENT EXAMPLE OF MEDICAL RESEARCH IN NEONATOLOGY

Extremely low birth weight infants are a particularly vulnerable population as they are in a high-risk category and thus prone to death or ongoing morbidities, including eye disease.[2] As part of standard medical care, extremely premature babies are provided with supplementary oxygen therapy post-birth. Previous professional practice standards recommended maintaining a baby's oxygen saturation range between 85 and 95%. However, researchers in the United States developing a study to ascertain appropriate levels of oxygen saturation in extremely low birth weight infants concluded that there was a lack of data about what level of saturation was most beneficial to babies within this broad range.[3] In 2005, this group of researchers began a study to address the perceived deficiency in knowledge. Their study, titled 'Surfactant, Positive Pressure, and Oxygenation Randomised Trial' (SUPPORT), compared lower versus higher ranges of oxygen saturation in such infants, to establish the range that would result in optimal outcomes. In particular, the researchers sought to establish the effect of saturation levels on survival, neurological development, and the likelihood of developing serious eye disorders such as retinopathy of prematurity.[4]

The SUPPORT study involved randomly assigning newborns to two groups.[5] The first group received 'high level oxygen', which involved maintaining oxygen saturation between 91% and 95%. The

[1] Tavernise S, "Study of Babies Did Not Disclose Risk, US Finds", *New York Times* (10 April 2013), http://www.nytimes.com/2013/04/11/health/parents-of-preemies-werent-told-of-risks-in-study.html?pagewanted=all&_r=0 viewed 24 May 2013.

[2] SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, "Target Ranges of Oxygen Saturation in Extremely Preterm Infants" (2010) 362(21) NEJM 1959 (SUPPORT Study Group).

[3] Drazen JM, Solomon CG and Greene MF, "Informed Consent and SUPPORT" (2013) 368(20) NEJM 1929.

[4] SUPPORT Study Group, n 2 at 1959-1969.

[5] SUPPORT Study Group, n 2 at 1959-1969.

second group received 'low level oxygen' to maintain a lower saturation (between 85% and 89%). The study was initiated by several prestigious universities in the United States of America, and later adopted by research centres in the United Kingdom, New Zealand and Australia (in a project titled 'Benefits of Oxygen Saturation Targeting' or 'BOOSTII').[6] As noted by Drazen et al, the willingness of other countries, including Australia, New Zealand and the United Kingdom, to adopt the same research question demonstrates the significance of the research and the importance given to addressing the deficit in empirical evidence.[7] Overall, 1,300 infants were recruited to the SUPPORT study during the period 2005-2009, with a further 2,315 infants recruited in Australia, New Zealand and the United Kingdom.[8]

The published outcomes of the SUPPORT study showed a significant statistical difference between outcomes for the two study arms, with the low-oxygen saturation infants having higher death and morbidity rates.[9] Concerns about the conduct of the study and allegations of non-compliance to ethical guidelines were raised with the United States Office for Human Research Protections after publication.[10] The Office subsequently reviewed the study and found that documents authorised by the original Institutional Review Board (IRB) and provided to parents of the infants involved in the SUPPORT study failed to include and adequately explain the potential for substantial risks to infants randomised to the lower-oxygen group. In particular, the documents failed to provide adequate disclosure of the higher risk of death and retinopathy of prematurity. Furthermore, the Office found problems with all the consent forms that were subsequently approved by the 22 other reviewing IRBs. Particular concerns included the failure of the researchers to inform parents that involvement in the study could result in their child receiving care that 'was different from what they would have received had they not participated in the study', and that the researchers should have had sufficient knowledge (based on the published data available) – before conducting the study – to warrant informing parents that involvement might make a difference to the chance of a child surviving or becoming blind.[11]

Despite the study being reviewed, approved and overseen by the IRBs of several leading United States institutions, and later, a number of Human Research Ethics Committees in Australia, New Zealand and United Kingdom, infants were recruited to the underperforming arm of the study for more than four years. The sister study, BOOSTII, was only suspended after its researchers – who had acted on the findings of the 2010 publication – conducted a preliminary review of their own data and discovered that lower saturation levels were associated with a higher rate of death in their study. At this point, recruitment to BOOSTII was suspended in Australia and the United Kingdom.[12]

These events highlight the need for ongoing scrutiny and monitoring, not only of medical research, but also of research oversight bodies and review procedures. This is particularly the case for therapeutic medical research that involves more than a minimal risk to participants, non-therapeutic medical research, and/or research involving vulnerable populations such as infants and children. This argument is supported by the fact that the primary aim of research oversight bodies and review boards such as HRECs is to protect and promote the wellbeing of research participants.[13]

APPROVAL OF MEDICAL RESEARCH IN AUSTRALIA

Understanding that involvement in medical research is a departure from conventional accepted clinical care is important.[14] By definition, the function of later-phase medical research studies (Phases II-IV) such as the SUPPORT and BOOSTII studies, is to test novel and potential treatments for their safety and efficacy in participants, and to contribute to new knowledge in the hope it will be of benefit in the future.[15] At the stage where these agents are being tested there is no scientific evidence either for or against the use of the agent in comparison to conventional accepted treatments. In

[6] SUPPORT Study Group, n 2 at 1959-1969.

[7] Drazen et al, n 3 at 1929-1931.

[8] Drazen et al, n 3 at 1929-1931.

[9] SUPPORT Study Group, n 2 at 1959-1969.

[10] Letter, Office of Human Research Protections [Re: Human Research Protections under Federalwide Assurance (FWA) 5960] (2013), http://www.hhs.gov/ohrp/detrm_letrs/YR13/mar13a.pdf viewed 24 May 2013.

[11] Letter, Office of Human Research Protections, n 10.

[12] Stenson B, Brocklehurst P and Tarnow-Mordi W, "Increased 36-Week Survival with High Oxygen Saturation Target in Extremely Preterm Infants" (2011) 364(17) NEJM 1680.

[13] National Health and Medical Research Council, Australian Research Council and Australian Vice-Chancellors' Committee, *National Statement on Ethical Conduct in Human Research* (National Health and Medical Research Council, Canberra, 2007) (National Statement).

[14] Miller FG and Joffe S, "Benefit in Phase 1 Oncology Trials: Therapeutic Misconception or Reasonable Treatment Option?" (2008) 5(6) *Clinical Trials* 617.

[15] Lewens T, "Distinguishing Treatment from Research: A Functional Approach" (2006) 32 *Journal of Medical Ethics* 424; Keech A, Gebski V and Pike R, *Interpreting and Reporting Clinical Trials. A Guide to the CONSORT Statement and the Principles of Randomised Controlled Trials* (Australian Medical Publishing, Sydney, 2007).

contrast, the function of early phase studies (Phase 0-I) is solely to establish safety and toxicities. These studies do not measure efficacy in the form of some treatment benefit for an illness or condition. Such studies are non-therapeutic and represent a very significant departure from patient-orientated clinical care, which has a therapeutic intent.[16]

In Australia, competent adults have the right to decide whether or not to consent to medical research. Those who consent often do so either because they wish to personally benefit by finding a new way to manage or cure their condition, or alternatively because they wish to contribute to new knowledge about an illness or condition.[17] As with the provision of medical care, medical practitioners undertaking medical research owe a legal duty of care to those involved in such research as well as a requirement to comply with ethical standards arising from research guidelines prescribed by the National Health and Medical Council of Australia (NHMRC) and respective funding bodies.[18] Before a research project can begin, it is necessary to obtain an independent, ethical review from a Human Research Ethics Committee (HREC). HRECs reviewing medical research are constituted according to NHMRC guidelines and include a representative sampling of key research stakeholders such as laypersons, lawyers, experts in research and clinical care, and counsellors.[19]

When researchers are seeking to recruit incompetent *adults*, an extra safeguard or independent review process is required in some jurisdictions. For example, in Queensland, according to the terms of the *Guardianship and Administration Act 2000* (Qld), s 72, approval must be obtained from the Queensland Civil and Administrative Tribunal for the involvement of incompetent adults in special medical research or experimental health care. Similar requirements for the mandatory review of medical research studies apply in some other States and Territories.[20] In Victoria, incompetent persons are able to be involved in medical research provided that a four-step process is satisfied, as stipulated under the *Guardianship and Administration Act 1986* (Vic). Of significance is the fact that the research must be approved by a relevant HREC,[21] that the participant is unlikely to recover within a reasonable time so that he or she can provide her or his own consent,[22] that consent is obtained from the surrogate decision-maker (referred to as the 'person responsible' under the Act),[23] or in cases where the 'person responsible' cannot be ascertained or contacted, a medical practitioner is able to carry out the research without consent if a number of further criteria are met.[24]

It is without doubt that later-phase medical research involving incompetent adults, as described in the introduction, would fall within the relevant procedural safeguard as outlined in the categories above. However, there appears be a lack of clarity around the consideration of early-phase studies that are not designed to be of personal benefit to participants, and have the potential for significant risk.[25] In cases where no likelihood of benefit can be established for an incompetent adult participant, it is unlikely that a tribunal would approve medical research involving that individual.[26] The extra

[16] Fleming T and DeMets D, "Surrogate Endpoints in Clincal Trials: Are We Being Misled?" (1996) 125 *Annals of Internal Medicine* 605; Kimmelman J, *Gene Transfer and the Ethics of First-in-Human Research: Lost in Translation* (Cambridge University Press. Cambridge, 2012); Miller and Joffe, n 14 at 617-623.

[17] Meropol N, Weinfurt K, Burnett C, Balsheim A, Benson A and Castel I, "Perceptions of Patients and Physicians Regarding Phase I Cancer Clinical Trials: Implications for Physician-Patient Communication" (2003) 21(13) *Journal of Clinical Oncology* 2589.

[18] National Health and Medical Research Council, *Australian Code for the Responsible Conduct of Research* (NHMRC, Canberra, 2007) Pt A, s 1.4 and Pt B, s 9.3.

[19] National Statement, n 13, p 81 at [5.1.30].

[20] Currently the ethical and scientific review of medical research is not regulated under Commonwealth laws. See *Guardianship Act 1987* (NSW), ss 45AA, 45AB; *Children and Young People Act 2008* (ACT) ss 807, 809; *Powers of Attorney Act 2006* (ACT), ss 35, 37(1)(d); In the Northern Territory a full guardianship order provides guardians with all powers to consent to health care if it is in the best interest of person being represented. However, a court order may be required for participation in clinical trials: see *Adult Guardianship Act* (NT), s 21, 'Major medical procedure'. The requirement for review of medical research involving incompetent adults varies between jurisdictions and is overly complex. Furthermore, no distinction is made between involvement in therapeutic research, which may be expected to benefit a person (for example, phase II-IV studies), and non-therapeutic research, where safety and toxicity are being established and no benefit is functionally intended.

[21] *Guardianship and Administration Act 1986* (Vic), s 42Q.

[22] *Guardianship and Administration Act 1986* (Vic), s 42R.

[23] *Guardianship and Administration Act 1986* (Vic), s 42S.

[24] *Guardianship and Administration Act 1986* (Vic), s 42T. Section 42T(2)(f) states that the clinician must believe, on reasonable grounds, that '(i) one of the purposes of the relevant research project is to assess the effectiveness of the therapy being researched; and (ii) the medical research procedure poses no more of a risk to the patient than the risk that is inherent in the patient's condition and alternative treatment', and according to s 42T(2)(g), that 'the practitioner believes on reasonable grounds that the relevant research project is based on valid scientific hypotheses that support a reasonable possibility of benefit for the patient as compared with standard treatment'.

[25] Lewens, n 15 at 424-429; Keech et al, n 15.

[26] See eg the *Guardianship and Administration Act 2000* (Qld), s 72(2), which states that for approval to be given by the Queensland Civil and Administrative Tribunal, '(b) the risk and inconvenience to the adult and the adult's quality of life is small; (c) the special medical research or experimental health care may result in significant benefit to the adult; (d) the potential benefit cannot be achieved in another way'.

mandatory review process for medical research involving incompetent adults in some jurisdictions provides a basis upon which to argue that early-phase, non-therapeutic research is classed as a special category of intervention, for which medical practitioners and researchers must gain approval. Furthermore, these requirements provide an objective, independent, review process, which recognises the inherent tensions involved for surrogate-decision-makers and the medical practitioners who are responsible for making decisions concerning the care of incompetent adult patients.

The legal position in Australia concerning medical research involving incompetent adults, as outlined above, highlights a concerning discrepancy. The requirements relating to the approval of medical research involving incompetent adults, and medical research involving children, are inconsistent. Unlike the position concerning adults, there are no similar safeguards under Australian law in relation to the approval of medical research involving children.

DISCUSSION

Ethical justification for medical research

The ethical acceptability of medical research studies that involve subjecting participants to potential risks and harm is dependent on the integrity of the processes that enable autonomous and informed decision-making, ie the consent process. For consent to be considered valid, potential participants (or their surrogate decision-makers) must be given sufficient information and the information must be understood. In the context of medical research, this includes an understanding of the function of such research and the potential risks and benefits.[27]

The concept of autonomy, however, is dependent on the ability of a person to make a free and independent decision.[28] In cases where researchers aim to recruit incompetent participants such as adults at the end of life, or children, the responsibility for making decisions about research participation falls to the surrogate decision-maker(s). For younger children and infants, this will normally be the child's parent(s). In the context of an incompetent adult, the surrogate decision-maker will usually be a close family member, such as a spouse, parent, sibling or adult child. Decisions concerning such individuals must be exercised in accordance with the person's best interests.[29]

Therefore, when making decisions about prospective treatments and/or medical research concerning children, parents must consider the potential benefits and the very real prospect of any burdens or risks associated with such interventions. As noted by Kerridge, Lowe and Stewart, responsibility lies with health care professionals, including those involved in recruiting children to research, to ensure that parents are making 'reasonable' choices that are based on what is in the best interests of a particular child.[30] This concept is known as the 'rational parent' standard, with commentators noting that 'a rational-parent standard requires the surrogate to demonstrate the ability to prioritise options for the child'.[31]

Young children are particularly vulnerable as they lack the physical and mental maturity to make decisions for themselves.[32] This status affords children a right to extra protection, a position that is adopted, eg, in Art 3 of the United Nations *Convention of the Rights of the Child.*[33] However, under Australian law, there is currently no statutory safeguard to ensure that children involved in medical research are protected in the same way as adults are in some jurisdictions. There is a need for such a

[27] Freedman B, Fuks A and Weijer C, "In Loco Parentis: Minimal Risk as an Ethical Threshold for Research upon Children" (1993) 23(2) *Hastings Center Report* 13 (Expanded Academic); Kerridge I, Lowe M and Stewart C, *Ethics and Law for the Health Professions* (4th ed, Federation Press, Leichhardt, 2013); Miller and Joffe, n 14 at 617-623.

[28] Maclean A, *Autonomy, Informed Consent and Medical Law: A Relational Challenge* (Cambridge University Press, Cambridge, 2009).

[29] Kerridge et al, n 28; Skene L, *Law and Medical Practice: Rights, Duties, Claims and Defences* (3rd ed, LexisNexis Butterworths, Melbourne, 2008). For a discussion of how the concept of "best interests" may be applied in the context of children who are involved in experimental research, see Elliston S, *The Best Interests of the Child in Healthcare* (Routledge, Abingdon, 2007) pp 191-242.

[30] The concept of 'reasonable choices' remains vague. However, generally speaking, choices are seen to be reasonable provided they fall within the acceptable thresholds for moral and legal reasons.

[31] Kerridge et al, n 28, p 481.

[32] Kerridge et al, n 28.

[33] Article 3 states: "In all actions concerning children, whether undertaken by public or private social welfare institutions, courts of law, administrative authorities or legislative bodies, the best interests of the child shall be a primary consideration". See United Nations, *Convention on the Rights of the Child*, Adopted and Opened for Signature, Ratification and Accession by General Assembly Resolution 44/25 of 20 November 1989; entry into force 2 September 1990, in accordance with Article 49 (1990). This extension to the particular rights of children is also reflected in the *Geneva Declaration of the Rights of the Child* of 1924; the *Declaration of the Rights of the Child* adopted by the General Assembly on 20 November 1959; the *Universal Declaration of Human Rights*; the *International Covenant on Civil and Political Rights* (mainly Art 23 and 24); and the *International Covenant on Economic, Social and Cultural Rights* (in particular, Art 10)

requirement within the law, as it is necessary to safeguard the interests and wellbeing of children so that they are not exposed to harmful research that is unlikely to be of therapeutic benefit to them. This is not a radical proposition, as it is generally accepted that such a safeguard is necessary in relation to incompetent adults.

Demonstrating the discrepancy in the review process for gaining approval of medical research studies in Australia

The incongruence between the current approaches to the review of medical research involving incompetent individuals is best illustrated in considering the requirements in Queensland for gaining approval of a medical research study involving a young infant participant, and the requirements in relation to an 18-year-old participant who lacks decision-making capacity. Medical researchers aiming to recruit the infant would be required to gain ethics approval for the study from a HREC, *before* approaching the parents for consent. In contrast, researchers aiming to recruit the 18-year-old would be required to submit their study for review by a HREC, *and* also gain approval from the Queensland Civil and Administrative Tribunal for the participant to be involved.

The review processes outlined above therefore appear to be inconsistent. This difference in approach requires some reasonable justification for research involving children being subject to a less rigorous review process.[34] This is particularly problematic given that children are generally considered to be more vulnerable than adults.[35] It is for this reason that a more rigorous review process in the context of medical research (particularly early-phase research) involving children is needed.

IN CONCLUSION

Currently in Australia a discrepancy exists regarding requirements for the review of medical research involving incompetent adults and requirements for the review of medical research involving children. Generally speaking, society regards children as being a special and vulnerable population. This special status affords children the right to be treated equally unless some reasonable justification exists. This includes the right to any protections afforded to other persons in similar positions, eg, the more rigorous review processes for medical research involving incompetent adults.

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[34] Rawls introduced the idea of "reflective equilibrium": where inequality exists, some reasonable justification of differences ought to be provided. See Rawls J, *A Theory of Justice* (Belknap Press of Harvard University Press, 1999). Dworkin also argued for a fundamental right to equal concern: see Dworkin R, *Taking Rights Seriously* (Duckworth, London, 1978) p 272. See also Freeman M, *The Rights and Wrongs of Children* (Francis Pinter, London, 1985).

[35] Kerridge et al, n 28.